



Clinical trial results:

A Multicenter, Multinational, Phase II Study to Evaluate Perjeta in Combination With Herceptin and Standard Neoadjuvant Anthracycline-Based Chemotherapy in Patients With HER2-Positive, Locally Advanced, Inflammatory, or Early-Stage Breast Cancer

Summary

EudraCT number	2014-000156-28
Trial protocol	DE GB ES IT PT FR PL DK
Global end of trial date	

Results information

Result version number	v1
This version publication date	17 March 2017
First version publication date	17 March 2017

Trial information

Trial identification

Sponsor protocol code	WO29217
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02132949
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F.Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F.Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F.Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	03 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 March 2016
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

This is a non-randomized, open-label, multicenter, multinational, Phase 2 trial including two parallel groups of participants. Objectives of the study included evaluation of cardiac safety, safety profiles of the two treatment regimens during the neoadjuvant and adjuvant treatment periods, and assessment of anti-tumor activity, clinical response, event-free survival (EFS), invasive disease-free survival (iDFS), and overall survival (OS) for each treatment regimen. Treatment regimens included a) dose-dense doxorubicin and cyclophosphamide (ddAC), followed by paclitaxel with pertuzumab and trastuzumab and b) 5-fluorouracil, epirubicin and cyclophosphamide (FEC), followed by docetaxel with pertuzumab and trastuzumab.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 July 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 91
Country: Number of subjects enrolled	Canada: 21
Country: Number of subjects enrolled	Denmark: 15
Country: Number of subjects enrolled	France: 75
Country: Number of subjects enrolled	United Kingdom: 34
Country: Number of subjects enrolled	Germany: 29
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	Mexico: 6
Country: Number of subjects enrolled	Norway: 12
Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	Portugal: 31
Country: Number of subjects enrolled	Spain: 62
Worldwide total number of subjects	401
EEA total number of subjects	283

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	353
From 65 to 84 years	48
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 401 participants were enrolled, 199 in Cohort A and 202 in Cohort B. One participant in Cohort B who was human epidermal growth factor receptor 2 (HER2) negative and was enrolled by error, was excluded. Hence, 199 participants were included in Cohort A and 201 participants in Cohort B.

Period 1

Period 1 title	Neoadjuvant Treatment Period
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab

Arm description:

Participants received doxorubicin and cyclophosphamide every 2 weeks (q2w) for 4 cycles, followed by paclitaxel for 12 weeks, with pertuzumab and trastuzumab given every 3 weeks (q3w) (8 cycles of chemotherapy in total prior to surgery) from the start of paclitaxel.

Arm type	Experimental
Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	Adriamycin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received doxorubicin 60 milligrams per square meter (mg/m²) as an intravenous (IV) bolus over 3-5 minutes (min) or as an infusion over 15-30min q2w for 4 cycles.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received cyclophosphamide 600mg/m² IV bolus over 3-5min or as an infusion, in accordance with local policy, q2w for 4 cycles.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received paclitaxel 80mg/m² IV infusion weekly once (qw) for 12 weeks.

Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	
Other name	Perjeta
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:	
Participants received pertuzumab 840mg loading dose IV, then 420mg IV q3w for 17 cycles.	
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	Herceptin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Participants received trastuzumab 8 milligrams per kilogram (mg/kg) loading dose IV, then 6mg/kg q3w for 17 cycles.	
Arm title	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab
Arm description:	
Participants received 5-fluorouracil, epirubicin, and cyclophosphamide given q3w for 4 cycles, followed by docetaxel q3w for 4 cycles, with pertuzumab and trastuzumab given q3w (8 cycles of chemotherapy in total prior to surgery) from the start of docetaxel.	
Arm type	Experimental
Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Participants received 5-fluorouracil 500mg/m ² as an IV bolus or as an infusion, in accordance with local policy, q3w for 4 cycles.	
Investigational medicinal product name	Epirubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Participants received epirubicin 100mg/m ² as an IV bolus over 3-5min or as an infusion over 3-5min, in accordance with local policy, q3w for 4 cycles.	
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Participants received docetaxel with starting dose of 75mg/m ² in Cycle 5, then 100mg/m ² for Cycles 6-8 q3w for 4 cycles.	
Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	
Other name	Perjeta
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Participants received pertuzumab 840mg loading dose IV, then 420mg IV q3w for 17 cycles.	
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	Herceptin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received trastuzumab 8 milligrams per kilogram (mg/kg) loading dose IV, then 6mg/kg q3w for 17 cycles.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received cyclophosphamide 600mg/m² IV bolus over 3-5min or as an infusion, in accordance with local policy, q2w for 4 cycles.

Number of subjects in period 1^[1]	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab
Started	199	201
Completed	182	189
Not completed	17	12
Consent withdrawn by subject	1	-
Physician decision	2	-
Early surgery	4	3
Adverse event	6	3
Reason unspecified	3	1
Withdrew prior to receiving study treatment	-	3
Disease Progression	1	1
Lack of efficacy	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: One participant in Cohort B, who was HER2 negative and was enrolled by error, was excluded. Thus, the number of subjects in the baseline period do not match with the worldwide number enrolled in the trial.

Period 2

Period 2 title	Adjuvant Treatment Period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab

Arm description:

Following surgery, participants received further adjuvant pertuzumab and trastuzumab q3w (13 cycles), such that a total of 17 cycles of pertuzumab and trastuzumab therapy are given during the study.

Arm type	Experimental
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Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	Adriamycin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received doxorubicin 60 milligrams per square meter (mg/m²) as an intravenous (IV) bolus over 3-5 minutes (min) or as an infusion over 15-30 min q2w for 4 cycles.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received cyclophosphamide 600 mg/m² IV bolus over 3-5 min or as an infusion, in accordance with local policy, q2w for 4 cycles.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received paclitaxel 80 mg/m² IV infusion weekly once (qw) for 12 weeks.

Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	
Other name	Perjeta
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received pertuzumab 840 mg loading dose IV, then 420 mg IV q3w for 17 cycles.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	Herceptin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received trastuzumab 8 milligrams per kilogram (mg/kg) loading dose IV, then 6 mg/kg q3w for 17 cycles.

Arm title	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab
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Arm description:

Following surgery, participants received further adjuvant pertuzumab and trastuzumab q3w (13 cycles), such that a total of 17 cycles of pertuzumab and trastuzumab therapy are given during the study.

Arm type	Experimental
Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received 5-fluorouracil 500 mg/m² as an IV bolus or as an infusion, in accordance with local policy, q3w for 4 cycles.

Investigational medicinal product name	Epirubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received epirubicin 100 mg/m² as an IV bolus over 3-5 min or as an infusion over 3-5 min, in accordance with local policy, q3w for 4 cycles.

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received docetaxel with starting dose of 75mg/m² in Cycle 5, then 100mg/m² for Cycles 6-8 q3w for 4 cycles.

Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	
Other name	Perjeta
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received pertuzumab 840 mg loading dose IV, then 420 mg IV q3w for 17 cycles.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	Herceptin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received trastuzumab 8 milligrams per kilogram (mg/kg) loading dose IV, then 6 mg/kg q3w for 17 cycles.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received cyclophosphamide 600 mg/m² IV bolus over 3-5 min or as an infusion, in accordance with local policy, q2w for 4 cycles.

Number of subjects in period 2	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab
Started	178	190
Completed	29	23
Not completed	149	167
Consent withdrawn by subject	1	1
Physician decision	1	-
Disease Relapse	-	1

Ongoing in Adjuvant Treatment	142	157
Protocol Deviation	1	-
Adverse event	4	6
Reason unspecified	-	1
Disease Progression	-	1

Baseline characteristics

Reporting groups

Reporting group title	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab
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Reporting group description:

Participants received doxorubicin and cyclophosphamide every 2 weeks (q2w) for 4 cycles, followed by paclitaxel for 12 weeks, with pertuzumab and trastuzumab given every 3 weeks (q3w) (8 cycles of chemotherapy in total prior to surgery) from the start of paclitaxel.

Reporting group title	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab
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Reporting group description:

Participants received 5-fluorouracil, epirubicin, and cyclophosphamide given q3w for 4 cycles, followed by docetaxel q3w for 4 cycles, with pertuzumab and trastuzumab given q3w (8 cycles of chemotherapy in total prior to surgery) from the start of docetaxel.

Reporting group values	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab	Total
Number of subjects	199	201	400
Age Categorical Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	49.8 ± 11.7	49.5 ± 11.5	-
Gender Categorical Units: Subjects			
Female	199	200	399
Male	0	1	1

End points

End points reporting groups

Reporting group title	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab
Reporting group description: Participants received doxorubicin and cyclophosphamide every 2 weeks (q2w) for 4 cycles, followed by paclitaxel for 12 weeks, with pertuzumab and trastuzumab given every 3 weeks (q3w) (8 cycles of chemotherapy in total prior to surgery) from the start of paclitaxel.	
Reporting group title	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab
Reporting group description: Participants received 5-fluorouracil, epirubicin, and cyclophosphamide given q3w for 4 cycles, followed by docetaxel q3w for 4 cycles, with pertuzumab and trastuzumab given q3w (8 cycles of chemotherapy in total prior to surgery) from the start of docetaxel.	
Reporting group title	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab
Reporting group description: Following surgery, participants received further adjuvant pertuzumab and trastuzumab q3w (13 cycles), such that a total of 17 cycles of pertuzumab and trastuzumab therapy are given during the study.	
Reporting group title	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab
Reporting group description: Following surgery, participants received further adjuvant pertuzumab and trastuzumab q3w (13 cycles), such that a total of 17 cycles of pertuzumab and trastuzumab therapy are given during the study.	

Primary: Percentage of Participants with New York Heart Association (NYHA) Class III and IV Heart Failure during the Neoadjuvant Treatment Period

End point title	Percentage of Participants with New York Heart Association (NYHA) Class III and IV Heart Failure during the Neoadjuvant Treatment Period ^[1]
End point description: Symptomatic left ventricular systolic dysfunction (LVSD) is defined as heart failure. NYHA classifies participants' heart failure condition based on the participant's symptoms. Class III: marked limitation of the physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea. Class IV: Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases. 95 percent (%) confidence intervals (CIs) are calculated with the use of the Clopper-Pearson method. Safety analysis population included all participants who received any amount of study drug.	
End point type	Primary
End point timeframe: Baseline to 24 weeks	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this end point.

End point values	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	198		
Units: percentage of participants				
number (confidence interval 95%)	1.5 (0.31 to 4.34)	0 (0 to 1.85)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants with Drop in Left Ventricular Ejection Fraction (LVEF) of at least 10 Percentage Points from Baseline and to Below 50% During the Neoadjuvant Treatment Period

End point title	Percentage of Participants with Drop in Left Ventricular Ejection Fraction (LVEF) of at least 10 Percentage Points from Baseline and to Below 50% During the Neoadjuvant Treatment Period ^[2]
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End point description:

A confirmed event was defined as at least two consecutive readings of declines in LVEF. 95% CIs are calculated with the use of the Clopper-Pearson method. Safety analysis population was considered for analysis of this end point.

End point type	Primary
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End point timeframe:

Baseline to 24 weeks

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this end point.

End point values	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	198		
Units: percentage of participants				
number (confidence interval 95%)	6.5 (3.5 to 10.9)	2 (0.6 to 5.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with NYHA Class III and IV Heart Failure during the Adjuvant Treatment Period at Primary Completion Date (03 March 2016)

End point title	Percentage of Participants with NYHA Class III and IV Heart Failure during the Adjuvant Treatment Period at Primary Completion Date (03 March 2016)
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End point description:

LVSD is defined as heart failure. NYHA classifies participants' heart failure condition based on the participant's symptoms. Class III: marked limitation of the physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea. Class IV: Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases. 95% CIs will be calculated with the use of the Clopper-Pearson method. Safety

analysis population who have started adjuvant treatment and were analyzable at the clinical cut-off date (03 March 2016).

End point type	Secondary
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End point timeframe:

Cycle 9 to Cycle 21 (cycle length=3 weeks; up to approximately 8 months) up to clinical cut-off date, 03 March 2016 (Month 20)

End point values	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	190		
Units: percentage of participants				
number (confidence interval 95%)	0 (0 to 2.05)	0.5 (0.01 to 2.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Drop in LVEF of at least 10 Points from Baseline and to Below 50% During the Adjuvant Treatment Period at Primary Completion Date (03 March 2016)

End point title	Percentage of Participants with Drop in LVEF of at least 10 Points from Baseline and to Below 50% During the Adjuvant Treatment Period at Primary Completion Date (03 March 2016)
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End point description:

A confirmed event was defined as at least two consecutive readings of declines in LVEF. 95% CIs will be calculated with the use of the Clopper-Pearson method. Safety analysis population who have started adjuvant treatment and were analyzable at the clinical cut-off date (03 March 2016).

End point type	Secondary
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End point timeframe:

Cycle 9 to Cycle 21 (cycle length=3 weeks; up to approximately 8 months) up to clinical cut-off date, 03 March 2016 (Month 20)

End point values	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	190		
Units: percentage of participants				
number (confidence interval 95%)	5.1 (2.3 to 9.4)	6.8 (3.7 to 11.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with NYHA Class III and IV Heart Failure at the End of Study

End point title	Percentage of Participants with NYHA Class III and IV Heart Failure at the End of Study
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End point description:

LVSD is defined as heart failure. NYHA classifies participants' heart failure condition based on the participant's symptoms. Class III: marked limitation of the physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea. Class IV: Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases. 95% CIs will be calculated with the use of the Clopper-Pearson method.

End point type	Secondary
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End point timeframe:

Baseline up to approximately 6.5 years

End point values	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[3]	0 ^[4]		
Units: percentage of participants				
number (not applicable)				

Notes:

[3] - Because the study is ongoing, results of this end point are anticipated by December 2020.

[4] - Because the study is ongoing, results of this end point are anticipated by December 2020.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Drop in LVEF of at least 10 Points from Baseline and to Below 50% at the End of Study

End point title	Percentage of Participants with Drop in LVEF of at least 10 Points from Baseline and to Below 50% at the End of Study
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End point description:

A confirmed event was defined as at least two consecutive readings of declines in LVEF. 95% CIs will be calculated with the use of the Clopper-Pearson method.

End point type	Secondary
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End point timeframe:

Baseline up to approximately 6.5 years

End point values	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[5]	0 ^[6]		
Units: percentage of participants				
number (not applicable)				

Notes:

[5] - Because the study is ongoing, results of this end point are anticipated by December 2020.

[6] - Because the study is ongoing, results of this end point are anticipated by December 2020.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Anti-Therapeutic Antibodies (ATAs) to Pertuzumab

End point title	Percentage of Participants with Anti-Therapeutic Antibodies (ATAs) to Pertuzumab
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End point description:

ITT population included all participants who were enrolled correctly irrespective of whether they received study drug or not. Here, "number of subjects analyzed" include those who were evaluable for the end point.

End point type	Secondary
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End point timeframe:

Screening then prior to pertuzumab infusion (Hour 0) in Cycles 5, 14, 18 thereafter anytime between Cycle 8 Day 21 and surgery, up to treatment completion visit (cycle length=2-3 weeks; up to approximately 6.5 years)

End point values	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186	197		
Units: percentage of participants				
number (not applicable)	0	0.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Total Pathological Complete Response (tpCR) Evaluated at the Time of Surgery Based on Local Pathologist's Assessment

After Surgery

End point title	Percentage of Participants with Total Pathological Complete Response (tpCR) Evaluated at the Time of Surgery Based on Local Pathologist's Assessment After Surgery
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End point description:

tpCR is defined as the absence of any residual invasive cancer in the breast and the absence of any metastatic cells in the regional lymph nodes. ITT population

End point type	Secondary
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End point timeframe:

24 weeks after neoadjuvant therapy (Post 8 cycles of neo-adjuvant therapy [cycle length=2-3 weeks])

End point values	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	201		
Units: percentage of participants				
number (confidence interval 95%)	61.8 (54.67 to 68.59)	60.7 (53.58 to 67.49)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Clinical Response as Determined by the Investigator According to Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 During the Neoadjuvant Treatment Period

End point title	Percentage of Participants with Clinical Response as Determined by the Investigator According to Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 During the Neoadjuvant Treatment Period
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End point description:

Clinical response was classified as either complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). CR: disappearance of all target lesions; PR: at least a 30% decrease in the sum of the longest diameter compared to Baseline. SD: neither sufficient shrinkage to qualify for PR nor sufficient (20%) increase to qualify for disease progression, in addition to no new target lesions. PD: at least a 20% increase in the sum of the longest diameter, taking as reference the smallest sum of the longest diameter observed at previous tumor assessment, or the appearance of any new lesions. 95% CIs are calculated with the use of the Clopper-Pearson method. ITT population.

End point type	Secondary
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End point timeframe:

Baseline until disease progression or death due to any cause up to 24 weeks (assessed on Day 1 of Cycles 1-8 [cycle length=2-3 weeks])

End point values	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	201		
Units: percentage of participants				
number (confidence interval 95%)				
Complete response	39.7 (32.85 to 46.86)	23.9 (18.16 to 30.39)		
Partial response	27.6 (21.55 to 34.41)	36.3 (29.67 to 43.38)		
Stable disease	7 (3.9 to 11.52)	10 (6.18 to 14.95)		
Progressive disease	0.5 (0.01 to 2.77)	1 (0.12 to 3.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Event-Free Survival Determined by the Investigator According to RECIST v1.1

End point title	Event-Free Survival Determined by the Investigator According to RECIST v1.1
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End point description:

EFS is defined as the time from enrollment to the first occurrence of progressive disease, relapse, or death from any cause. PD: at least a 20% increase in the sum of the longest diameter, taking as reference the smallest sum of the longest diameter observed at previous tumor assessment, or the appearance of any new lesions.

End point type	Secondary
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End point timeframe:

Baseline until disease progression or death due to any cause up to approximately 6.5 years (assessed on Day 1 of Cycles 1-8 [cycle length=2-3 weeks] and every 3 months thereafter until study completion or early termination)

End point values	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[7]	0 ^[8]		
Units: months				
median (full range (min-max))	(to)	(to)		

Notes:

[7] - Because the study is ongoing, results of this end point are anticipated by December 2020.

[8] - Because the study is ongoing, results of this end point are anticipated by December 2020.

Statistical analyses

No statistical analyses for this end point

Secondary: Invasive Disease Free Survival (iDFS) Determined by the Investigator According to RECIST v1.1

End point title	Invasive Disease Free Survival (iDFS) Determined by the Investigator According to RECIST v1.1
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End point description:

iDFS is defined as the time from the first date of no disease (the date of surgery) to the first documentation of progressive invasive disease, relapse, or death. PD: at least a 20% increase in the sum of the longest diameter, taking as reference the smallest sum of the longest diameter observed at previous tumor assessment, or the appearance of any new lesions.

End point type	Secondary
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End point timeframe:

Baseline until disease progression or death due to any cause up to approximately 6.5 years (assessed on Day 1 of Cycles 1-8 [cycle length=2-3 weeks] and every 3 months thereafter until study completion or early termination)

End point values	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[9]	0 ^[10]		
Units: months				
median (full range (min-max))	(to)	(to)		

Notes:

[9] - Because the study is ongoing, results of this end point are anticipated by December 2020.

[10] - Because the study is ongoing, results of this end point are anticipated by December 2020.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival
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End point description:

OS was defined as the time from enrollment to death from any cause.

End point type	Secondary
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End point timeframe:

Baseline up to death (approximately 6.5 years)

End point values	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[11]	0 ^[12]		
Units: months				

median (full range (min-max))	(to)	(to)		
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Notes:

[11] - Because the study is ongoing, results of this end point are anticipated by December 2020.

[12] - Because the study is ongoing, results of this end point are anticipated by December 2020.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 24 weeks

Adverse event reporting additional description:

Safety analysis population. Reported adverse events data covers the safety information until the neoadjuvant period.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0.
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Reporting groups

Reporting group title	Cohort B: FEC+Docetaxel+Pertuzumab+Trastuzumab
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Reporting group description:

Participants received 5-fluorouracil, epirubicin, and cyclophosphamide given q3w for 4 cycles, followed by docetaxel q3w for 4 cycles, with pertuzumab and trastuzumab given q3w (8 cycles of chemotherapy in total prior to surgery) from the start of docetaxel. Following surgery, participants received/will receive further adjuvant pertuzumab and trastuzumab q3w (13 cycles), such that a total of 17 cycles of pertuzumab and trastuzumab therapy are given during the study.

Reporting group title	Cohort A: ddAC+Paclitaxel+Pertuzumab+Trastuzumab
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Reporting group description:

Participants received doxorubicin and cyclophosphamide every 2 weeks (q2w) for 4 cycles, followed by paclitaxel for 12 weeks, with pertuzumab and trastuzumab given every 3 weeks (q3w) (8 cycles of chemotherapy in total prior to surgery) from the start of paclitaxel. Following surgery, participants received/will receive further adjuvant pertuzumab and trastuzumab q3w (13 cycles), such that a total of 17 cycles of pertuzumab and trastuzumab therapy are given during the study.

Serious adverse events	Cohort B: FEC+Docetaxel+Pertuzumab+Trastuzumab	Cohort A: ddAC+Paclitaxel+Pertuzumab+Trastuzumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	52 / 198 (26.26%)	45 / 199 (22.61%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events			
Surgical and medical procedures			
Mastectomy			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			

subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 198 (2.02%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	4 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Breast haematoma			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	1 / 198 (0.51%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 198 (0.00%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	0 / 198 (0.00%)	3 / 199 (1.51%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			

subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	2 / 198 (1.01%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seroma			
subjects affected / exposed	1 / 198 (0.51%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 198 (0.00%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myocardial ischaemia			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Presyncope			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	27 / 198 (13.64%)	12 / 199 (6.03%)	
occurrences causally related to treatment / all	28 / 28	12 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 198 (1.01%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pancytopenia			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	11 / 198 (5.56%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	9 / 12	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Odynophagia			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Cholelithiasis			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema multiforme			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin necrosis			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 198 (0.00%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 198 (0.00%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	2 / 198 (1.01%)	4 / 199 (2.01%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			

subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	7 / 198 (3.54%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	7 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 198 (0.51%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal bacteraemia			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 198 (0.00%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			

subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cohort B: FEC+Docetaxel+Pertuzumab+Trastuzumab	Cohort A: ddAC+Paclitaxel+Pertuzumab+Trastuzumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	198 / 198 (100.00%)	197 / 199 (98.99%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	26 / 198 (13.13%)	38 / 199 (19.10%)	
occurrences (all)	27	39	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	82 / 198 (41.41%)	37 / 199 (18.59%)	
occurrences (all)	104	56	
Chills			
subjects affected / exposed	2 / 198 (1.01%)	13 / 199 (6.53%)	
occurrences (all)	2	15	
Fatigue			
subjects affected / exposed	76 / 198 (38.38%)	116 / 199 (58.29%)	
occurrences (all)	98	125	
Influenza like illness			
subjects affected / exposed	15 / 198 (7.58%)	2 / 199 (1.01%)	
occurrences (all)	16	2	
Mucosal inflammation			
subjects affected / exposed	74 / 198 (37.37%)	43 / 199 (21.61%)	
occurrences (all)	99	50	

Oedema peripheral subjects affected / exposed occurrences (all)	24 / 198 (12.12%) 27	18 / 199 (9.05%) 21	
Pain subjects affected / exposed occurrences (all)	4 / 198 (2.02%) 4	14 / 199 (7.04%) 14	
Pyrexia subjects affected / exposed occurrences (all)	31 / 198 (15.66%) 40	29 / 199 (14.57%) 32	
Reproductive system and breast disorders Breast pain subjects affected / exposed occurrences (all)	12 / 198 (6.06%) 12	13 / 199 (6.53%) 14	
Vulvovaginal dryness subjects affected / exposed occurrences (all)	4 / 198 (2.02%) 4	12 / 199 (6.03%) 12	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	17 / 198 (8.59%) 19	40 / 199 (20.10%) 44	
Dyspnoea subjects affected / exposed occurrences (all)	29 / 198 (14.65%) 30	28 / 199 (14.07%) 29	
Epistaxis subjects affected / exposed occurrences (all)	37 / 198 (18.69%) 38	50 / 199 (25.13%) 52	
Nasal congestion subjects affected / exposed occurrences (all)	2 / 198 (1.01%) 2	15 / 199 (7.54%) 15	
Oropharyngeal pain subjects affected / exposed occurrences (all)	15 / 198 (7.58%) 16	20 / 199 (10.05%) 22	
Upper-airway cough syndrome subjects affected / exposed occurrences (all)	0 / 198 (0.00%) 0	11 / 199 (5.53%) 12	
Rhinorrhoea			

subjects affected / exposed occurrences (all)	19 / 198 (9.60%) 19	12 / 199 (6.03%) 12	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	9 / 198 (4.55%)	17 / 199 (8.54%)	
occurrences (all)	9	18	
Depression			
subjects affected / exposed	4 / 198 (2.02%)	12 / 199 (6.03%)	
occurrences (all)	4	12	
Insomnia			
subjects affected / exposed	25 / 198 (12.63%)	37 / 199 (18.59%)	
occurrences (all)	27	40	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	10 / 198 (5.05%)	14 / 199 (7.04%)	
occurrences (all)	11	15	
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 198 (4.04%)	14 / 199 (7.04%)	
occurrences (all)	9	16	
Ejection fraction decreased			
subjects affected / exposed	7 / 198 (3.54%)	11 / 199 (5.53%)	
occurrences (all)	7	13	
Lymphocyte count decreased			
subjects affected / exposed	0 / 198 (0.00%)	10 / 199 (5.03%)	
occurrences (all)	0	10	
Neutrophil count decreased			
subjects affected / exposed	17 / 198 (8.59%)	17 / 199 (8.54%)	
occurrences (all)	20	20	
Weight decreased			
subjects affected / exposed	8 / 198 (4.04%)	13 / 199 (6.53%)	
occurrences (all)	8	13	
White blood cell count decreased			
subjects affected / exposed	5 / 198 (2.53%)	21 / 199 (10.55%)	
occurrences (all)	5	24	
Injury, poisoning and procedural complications			

Infusion related reaction subjects affected / exposed occurrences (all)	23 / 198 (11.62%) 27	31 / 199 (15.58%) 33	
Procedural pain subjects affected / exposed occurrences (all)	8 / 198 (4.04%) 8	15 / 199 (7.54%) 15	
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	15 / 198 (7.58%) 17	23 / 199 (11.56%) 28	
Dysgeusia subjects affected / exposed occurrences (all)	38 / 198 (19.19%) 44	39 / 199 (19.60%) 42	
Headache subjects affected / exposed occurrences (all)	28 / 198 (14.14%) 32	60 / 199 (30.15%) 70	
Hypoaesthesia subjects affected / exposed occurrences (all)	7 / 198 (3.54%) 7	11 / 199 (5.53%) 11	
Neuropathy peripheral subjects affected / exposed occurrences (all)	26 / 198 (13.13%) 28	46 / 199 (23.12%) 47	
Paraesthesia subjects affected / exposed occurrences (all)	18 / 198 (9.09%) 20	29 / 199 (14.57%) 33	
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	15 / 198 (7.58%) 17	38 / 199 (19.10%) 41	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	60 / 198 (30.30%) 67	54 / 199 (27.14%) 62	
Neutropenia subjects affected / exposed occurrences (all)	31 / 198 (15.66%) 40	42 / 199 (21.11%) 52	
Eye disorders			

Dry eye			
subjects affected / exposed	10 / 198 (5.05%)	12 / 199 (6.03%)	
occurrences (all)	10	12	
Lacrimation increased			
subjects affected / exposed	36 / 198 (18.18%)	18 / 199 (9.05%)	
occurrences (all)	36	18	
Vision blurred			
subjects affected / exposed	1 / 198 (0.51%)	13 / 199 (6.53%)	
occurrences (all)	1	14	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	20 / 198 (10.10%)	10 / 199 (5.03%)	
occurrences (all)	21	10	
Abdominal pain upper			
subjects affected / exposed	26 / 198 (13.13%)	12 / 199 (6.03%)	
occurrences (all)	28	12	
Constipation			
subjects affected / exposed	76 / 198 (38.38%)	69 / 199 (34.67%)	
occurrences (all)	86	78	
Diarrhoea			
subjects affected / exposed	130 / 198 (65.66%)	132 / 199 (66.33%)	
occurrences (all)	176	179	
Dry mouth			
subjects affected / exposed	14 / 198 (7.07%)	9 / 199 (4.52%)	
occurrences (all)	14	9	
Dyspepsia			
subjects affected / exposed	32 / 198 (16.16%)	38 / 199 (19.10%)	
occurrences (all)	36	41	
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 198 (2.02%)	23 / 199 (11.56%)	
occurrences (all)	4	23	
Haemorrhoids			
subjects affected / exposed	17 / 198 (8.59%)	16 / 199 (8.04%)	
occurrences (all)	19	16	
Mouth ulceration			

subjects affected / exposed	12 / 198 (6.06%)	5 / 199 (2.51%)	
occurrences (all)	13	5	
Nausea			
subjects affected / exposed	137 / 198 (69.19%)	141 / 199 (70.85%)	
occurrences (all)	182	166	
Stomatitis			
subjects affected / exposed	54 / 198 (27.27%)	49 / 199 (24.62%)	
occurrences (all)	67	54	
Vomiting			
subjects affected / exposed	69 / 198 (34.85%)	45 / 199 (22.61%)	
occurrences (all)	96	50	
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	6 / 198 (3.03%)	11 / 199 (5.53%)	
occurrences (all)	6	14	
Alopecia			
subjects affected / exposed	116 / 198 (58.59%)	124 / 199 (62.31%)	
occurrences (all)	117	124	
Dry skin			
subjects affected / exposed	19 / 198 (9.60%)	27 / 199 (13.57%)	
occurrences (all)	20	27	
Erythema			
subjects affected / exposed	11 / 198 (5.56%)	3 / 199 (1.51%)	
occurrences (all)	14	3	
Nail discolouration			
subjects affected / exposed	3 / 198 (1.52%)	29 / 199 (14.57%)	
occurrences (all)	3	29	
Nail disorder			
subjects affected / exposed	19 / 198 (9.60%)	14 / 199 (7.04%)	
occurrences (all)	19	14	
Onycholysis			
subjects affected / exposed	9 / 198 (4.55%)	11 / 199 (5.53%)	
occurrences (all)	9	12	
Onychomadesis			
subjects affected / exposed	1 / 198 (0.51%)	18 / 199 (9.05%)	
occurrences (all)	1	18	

Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	20 / 198 (10.10%)	11 / 199 (5.53%)	
occurrences (all)	20	11	
Pruritus			
subjects affected / exposed	16 / 198 (8.08%)	15 / 199 (7.54%)	
occurrences (all)	18	16	
Rash			
subjects affected / exposed	21 / 198 (10.61%)	28 / 199 (14.07%)	
occurrences (all)	22	31	
Rash maculo-papular			
subjects affected / exposed	1 / 198 (0.51%)	16 / 199 (8.04%)	
occurrences (all)	1	16	
Skin hyperpigmentation			
subjects affected / exposed	3 / 198 (1.52%)	10 / 199 (5.03%)	
occurrences (all)	3	10	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 198 (1.01%)	13 / 199 (6.53%)	
occurrences (all)	2	14	
Pollakiuria			
subjects affected / exposed	2 / 198 (1.01%)	12 / 199 (6.03%)	
occurrences (all)	2	13	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	42 / 198 (21.21%)	39 / 199 (19.60%)	
occurrences (all)	48	44	
Back pain			
subjects affected / exposed	17 / 198 (8.59%)	20 / 199 (10.05%)	
occurrences (all)	18	23	
Bone pain			
subjects affected / exposed	9 / 198 (4.55%)	23 / 199 (11.56%)	
occurrences (all)	13	26	
Muscle spasms			
subjects affected / exposed	2 / 198 (1.01%)	15 / 199 (7.54%)	
occurrences (all)	2	15	
Musculoskeletal pain			

subjects affected / exposed occurrences (all)	10 / 198 (5.05%) 10	9 / 199 (4.52%) 9	
Myalgia subjects affected / exposed occurrences (all)	66 / 198 (33.33%) 80	40 / 199 (20.10%) 43	
Pain in extremity subjects affected / exposed occurrences (all)	15 / 198 (7.58%) 17	20 / 199 (10.05%) 20	
Infections and infestations			
Conjunctivitis subjects affected / exposed occurrences (all)	16 / 198 (8.08%) 16	8 / 199 (4.02%) 8	
Nasopharyngitis subjects affected / exposed occurrences (all)	17 / 198 (8.59%) 18	14 / 199 (7.04%) 16	
Oral candidiasis subjects affected / exposed occurrences (all)	11 / 198 (5.56%) 11	1 / 199 (0.50%) 1	
Rhinitis subjects affected / exposed occurrences (all)	14 / 198 (7.07%) 14	6 / 199 (3.02%) 6	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	4 / 198 (2.02%) 4	14 / 199 (7.04%) 15	
Urinary tract infection subjects affected / exposed occurrences (all)	4 / 198 (2.02%) 4	19 / 199 (9.55%) 22	
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	45 / 198 (22.73%) 48	39 / 199 (19.60%) 41	
Dehydration subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1	10 / 199 (5.03%) 14	
Hypokalaemia			

subjects affected / exposed	5 / 198 (2.53%)	14 / 199 (7.04%)	
occurrences (all)	6	15	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 February 2014	It was amended to extend the duration of reporting pregnancy and the time of prohibition of breast feeding to 7 months after receipt of the final dose of study drug.
17 June 2014	The protocol was updated to specify that anti-HER2 treatment should not start if the LVEF is <50% after anthracycline treatment for participants in both Cohorts A and B. The echocardiogram (ECHO)/multiple gated acquisition scan (MUGA) assessment at Cycle 3 or 4 has been removed to be more in line with clinical practice.
26 May 2016	A minor modification of the exclusion criterion regarding history of malignancy has been made for alignment with current clinical practice. Clarification that participants with prior breast malignancies within 5 years of study entry should be excluded was made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study is still ongoing and the results are based on the primary analysis (clinical cutoff date of 03 March 2016). Full data from the adjuvant and treatment-free follow-up periods are anticipated by December 2020.

Notes: